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(54) Title: METHODS FOR THE TREATMENT OF THE CENTRAL NERVOUS SYSTEM OR EYE INVOLVING PATHOGENIC OXIDATION PATHWAYS (57) Abstract A composition and method for the treatment of traumatic injuries and acute or chronic disorders of the central nervous system and the eye, including the retina and optic nerve, that are mediated by pathogenic oxidation processes that includes the administration of an effective amount of a lipid soluble thioester or thioether of N-acetylcysteine.		

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METHODS FOR THE TREATMENT OF THE CENTRAL NERVOUS SYSTEM OR EYE INVOLVING PATHOGENIC OXIDATION PATHWAYS

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This invention is a method for the treatment of traumatic injury or disorders involving pathogenic oxidation pathways that affect the brain, spinal cord, or the eye, including the retina and optic nerve, which includes the administration of an effective amount of a lipid soluble thioester or thioether of N-acetylcysteine or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

Background of the Invention

One of the primary processes which contributes to injury to nerves in the brain or spinal cord (the central nervous system, referred to below as the CNS), as well as to ocular tissue, including the retina and optic nerve, is believed to be pathogenic oxidation reactions that are associated with the presence or production of reactive oxygen species, and notably, oxygen free radicals.

Oxygen toxicity can occur, among other ways, through the degradation of atmospheric oxygen (O_2) or the degradation of reactive oxygen-containing species (such as peroxides, e.g., H_2O_2) to oxygen free radicals (such as hydroxyl radicals, i.e., $\bullet OH$). These reactive species can mediate a wide variety of pathogenic oxidative processes, including the oxidization of thiol groups of important cellular enzymes and proteins, the damage or scission of nucleic acids, and the peroxidation of polyunsaturated membrane lipids, which in turn can induce a series of other cellular changes that can result in cell injury and death.

The body defends itself from these events both enzymatically (glutathione peroxidase, glutathione reductase, catalase, and superoxide dismutase) and through the use of antioxidants (such as vitamin E and glutathione). Glutathione is the key substrate in a reaction that is catalyzed by glutathione peroxidase and which eliminates hydrogen peroxide and lipid peroxides formed by oxygen radicals. Therefore, increased levels of glutathione are thought to protect the body against free radical-induced injury. In one study, increased glutathione levels were shown to increase the survival time of mice or rats which were housed in atmospheres containing increased partial pressures of oxygen (Gerschman, R. et al, *Amer. J. Physiol.*, 1958, 192, 563-571; Sanders, A.P., et al, *Aerospace Med.*, 1972, 43, 533-536).

A number of antioxidants have been evaluated as alternatives to corticosteroids for the treatment of a variety of conditions which are associated with oxygen mediated CNS and spinal cord damage. For example, in animal models, lipid peroxidation can be inhibited by pharmacological agents with antioxidant properties such as methylprednisolone or tirilazad mesylate.

A major problem in treating traumatic injury and other disorders of the central nervous system is the presence of the blood-brain barrier (BBB) which imposes limitations on the transportability of potential therapeutic agents from the plasma to the extracellular fluids of the brain and spinal cord.

To traverse the CNS vasculature, a drug must first leave the plasma. The drug can then enter the capillary endothelial cell membrane, leave the membrane and enter the cytoplasm. Finally, the drug is conveyed through the outer cell membrane to

the surrounding extracellular fluid in the brain. An alternative pathway for drug transport is via the inter-endothelial cell junction.

In order to accomplish this passage through the CNS vasculature, the molecule must possess certain physical and chemical characteristics. Most notably, the molecule must be soluble in a non-polar (lipophilic) environment. A certain degree of water solubility is required, however, for a drug to be transported via the plasma to the brain. Similarly, drugs must be substantially lipid soluble to pass through the ocular tissue for treatment of the eye, but it may be advantageous for the drug to have a degree of water solubility to pass through the aqueous humor within the eye itself.

Lalitha et al., have attempted to increase the glutathione levels in the brains of mice exposed to high pressures of oxygen by administration of N-acetylcysteine through drinking water and intraperitoneal injections (Lalitha, T., et al, *Pharmacology and Toxicology*, 1990, 66, 56-61). Although glutathione levels in other organs were increased, the study did not find any alteration of glutathione levels in the brains of oxygen exposed or unexposed mice after treatment with N-acetylcysteine. The study concluded that extracerebral increases in glutathione levels did not protect against oxygen induced CNS toxicity. Because N-acetylcysteine is known to increase the biosynthesis of glutathione, the lack of an increase in brain glutathione in this study was thought to be due to either the short duration of the treatment and/or the inability of the drug to cross the blood-brain barrier (Lalitha, T., et al, *Pharmacology and Toxicology*, 1990, 66, 56-61).

Head or Spinal Cord Traumatic Injuries

In patients with head or spinal cord traumatic injuries, the development of neurological dysfunction is believed to be caused primarily by nerve cell damage and death caused by peroxidation of lipids. Oxygen radicals are known to be formed after traumatic CNS injury, and during reperfusion following obstruction of CNS blood flow. One important mechanism by which free radicals are formed in the CNS immediately following experimental injury probably involves the cyclo-oxygenase metabolism of arachadonic acid. Accordingly, drugs that can scavenge free radicals before, during or after CNS traumatic injury may minimize the extent of the neuronal damage which occurs in these settings.

Degenerative Central Nervous System Disorders

Degenerative central nervous system disorders have also been linked to pathogenic oxidation processes.

The cause of Parkinson's disease (PD), an example of a degenerative central nervous system disorder, is currently thought to be progressive damage to neurons by one or more environmental toxins. The major visible symptoms of Parkinson's Disease (PD) are tremor and bradykinesia (slow movement).

Symptoms associated with naturally occurring Parkinsonism also develop in patients who have ingested illicitly synthesized meperidine which contains the contaminant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP can penetrate the blood-brain barrier (BBB) and is oxidized by monoamine oxidase type B (MAO-B) to form a metabolite that causes neuronal toxicity (Kikuchi, K. et al; *Drug Met. and Dispos.* 1991, 19(1), 257).

The degenerative progress of certain diseases

of the central nervous system, such as Parkinson's disease (PD), has been shown to be positively influenced by the presence of certain antioxidants, which delay the onset of symptoms.

- 5 One study has reported that α -tocopherol, β -carotene, ascorbic acid or N-acetylcysteine can partially protect mice that would normally exhibit symptoms similar to those of PD. It has also been reported that therapy which includes the drug
- 10 deprenyl, an antioxidant and selective MAO-B inhibitor, can slow the development of motor disability and the rate of disease progression when used in the early stages of PD (Cecil Textbook of Medicine, 19th ed., Wyngaarden, J.B., Smith L.H.,
- 15 Bennett, J.C. Eds., Saunders: 1992, p. 2130).

Current treatment for Parkinson's Disease is aimed at decreasing the time of onset of tremor and bradykinesia. In patients seen early in the course of their disease, deprenyl is administered in

20 conjunction with an anticholinergic and tri-cyclic antidepressants. However, once symptoms become disruptive and unresponsive to treatment with deprenyl, L-dopa is prescribed, and the patient is then exposed to the numerous undesirable side

25 effects associated with the administration of this agent.

Alzheimer's disease is another example of a degenerative brain disease that is caused by a progressive and selective degeneration of neuron

30 populations in discrete portions of the brain. It is manifested clinically by an impairment of memory and decision-making that begins insidiously and progressively worsens. There is no cure for Alzheimer's disease, and no drug tried so far can

35 alter the progress of the disease (Cecil Textbook of Medicine, 19th ed., Wyngaarden, J.B., Smith L.H., Bennett, J.C. Eds., Saunders: 1992, p. 2075).

Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's Disease) is a fatal degenerative disease of the CNS. In the case of ALS, degeneration of the motor neurons of the spinal cord and the brain stem causes slow progressive paralysis of the voluntary muscles. There is also an inflammatory component to the pathology of the disease. (Cecil Textbook of Medicine, 19th ed., Wyngaarden, J.B., Smith L.H., Bennett, J.C. Eds., Saunders: Philadelphia, 1992, p. 2141).

Pathogenic Oxidation Processes in the Eye

Pathogenic oxidation processes can also cause damage to the eye. The aqueous humor of the eye includes a significant amount of hydrogen peroxide. The anterior tissues bathed by the aqueous humor, including the cornea and the anterior portion of the lens, therefore exist in an oxidative environment, and can be harmed when the hydrogen peroxide level is above normal. Exposure of the eye to light of certain wavelengths can also cause harm to anterior, posterior and other tissues of the eye, including the lens, retina and retinal pigmented epithelium.

Pathogenic ocular oxidation pathways can also be triggered in association with ischemia, a variety of drugs or endogenous cell regulators, or by pressure on tissues caused by pressure changes in the anterior chamber of the eye.

Oxidative ocular processes are specifically involved in age-related cataracts, light-induced retinal damage, other retinopathies such as diabetic retinopathy or age-related macular degeneration, inflammatory damage, vascular leakage and edema (as in cystoid macular edema), accidental or surgical trauma, angiogenesis, corneal opacities, retrolental fibroplasia, and some forms of glaucoma.

U.S. Patent Nos. 5,256,408 and 5,124,062 disclose that a group of amino-steroids are useful in the treatment of oxidative intraocular damage.

5 In light of the seriousness of traumatic injuries and disorders of the central nervous system and eye that are mediated by pathogenic oxidation processes, it would be of great value to have for their treatment a pharmaceutical agent and method that can be delivered effectively to the
10 site of potential oxidation.

It is therefore an object of the present invention to provide a compound, composition, and method for the treatment of traumatic injuries and disorders of the central nervous system and eye
15 that are mediated by pathogenic oxidation processes.

It is another object of the present invention to provide a compound and composition that can pass through the blood-brain barrier.

20 It is yet another object of the present invention to provide a compound and composition that is absorbed by the eye, and in particular, can pass into and through ocular tissue.

Summary of the Invention

25 Traumatic injuries and acute or chronic disorders of the central nervous system and the eye, including the retina and optic nerve, that are mediated by pathogenic oxidation processes can be treated by the administration of an effective
30 amount of a lipid soluble thioester or thioether of N-acetylcysteine (referred to below as NAC). In the preferred method of administration, the active compound or its pharmaceutically acceptable salt are administered in a suitable carrier for CNS or
35 ophthalmic delivery.

N-acetylcysteine acts as an antioxidant that minimizes the injurious effect of the pathogenic oxidizing species in the CNS or eye. It has been discovered that N-acetylcysteine itself is not an effective drug for the treatment of CNS or ocular oxidative injury or disorders because it is not sufficiently lipophilic to be absorbed into the appropriate regions. However, when NAC is derivatized as a lipophilic thioester or thioether, it passes efficiently into the CNS or eye. Therefore, these compounds represent a new prodrug form of NAC for the delivery of NAC to otherwise inaccessible regions of the body. Further, it has been found that thioester derivatives of NAC are stable in non-biological aqueous solutions such as saline, phosphate-buffered saline, lactated Ringer solution, sterile water, and water-containing creams, gels, lotions, solutions, foams and suspensions. However, in biological fluids such as plasma or tissues the thioester derivative of NAC is converted to the parent N-acetylcysteine that exhibits the desired antioxidant properties.

The delivery of N-acetylcysteine through the blood-brain barrier in the form of a thioester or thioether is useful in the treatment of symptoms associated with Parkinson's Disease, Alzheimer's Disease, Huntington's syndrome, amyotrophic lateral sclerosis, acute traumatic spinal cord and brain injury, or other degenerative diseases of the CNS, or in the treatment of CNS trauma.

N-acetylcysteine exhibits low toxicity in vivo, and is significantly less toxic than deprenyl (for example, the LD₅₀ in rats has been measured at 1140 or 81 mg/kg intravenously, for N-acetylcysteine or deprenyl, respectively).

The invention also provides a compound and method for the improvement of visual function or

for the prevention or minimization of loss of visual function in the eye of a host which is subject to oxidative intraocular damage.

Specifically, methods and compounds are provided that enhance the ability of the tissue of the eye to withstand trauma, surgery, the threat of glaucoma associated with increasing intraocular pressure, or to resist the potential loss of vision from progression of macular degeneration and the like, by supplementing, both acutely and chronically, the natural ability of the eye to resist oxidative damage.

The thioesters or thioethers of NAC are useful in treating the symptoms of a wide variety of ocular injuries and disorders that are mediated by pathogenic oxidative processes, including but not limited to optic neuritis, retrobulbar neuritis, inherited optic atrophies, diabetic retinopathy, cataract formation, glaucoma or the risk of glaucoma associated with significantly elevated intraocular pressure, inflammatory eye disease, retinal eye disease, intraocular pressure rise due to uveitis, post-infarct amblyopia, traumatic eye injury (such as blunt trauma, compression injury, hyphema, surgical trauma, etc.), neovascular or ischemic eye disease (including conditions in the eye involving local ischemia such as corneal edema from prolonged wearing of contact lenses and the like), bullous keratitis, dry eye including keratoconjunctivitis sicca (Sjogren's syndrome), alkali burn, and conditions arising from transplantation of a corneal graft or transplantation of ocular cells.

Detailed Description of the Invention

The term alkyl, as used herein, refers to a saturated straight, branched, or cyclic (or a combination thereof) hydrocarbon of C_1 to C_{22} , and specifically includes methyl, ethyl, propyl, isopropyl, cyclopropylmethyl, cyclobutylmethyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, heptyl, octyl, nonyl, and decyl.

The term aryl, as used herein, refers to phenyl, or substituted phenyl, wherein the substituent is halo, alkyl, alkoxy, alkylthio, haloalkyl, hydroxyalkyl, alkoxyalkyl, methylenedioxy, cyano, $C(O)(alkyl)$, carboxylic acid, CO_2alkyl , amide, amino, alkylamino or dialkylamino, and wherein the aryl group can have up to 3 substituents.

The term aralkyl refers to an aryl group with an alkyl substituent.

The term alkaryl refers to an alkyl group with an aryl substituent, including benzyl, substituted benzyl, phenethyl or substituted phenethyl, wherein the substituents are as defined above for aryl groups.

As used herein the term fatty acid refers to a long chain (C_6 to C_{24}) aliphatic carboxylic acid.

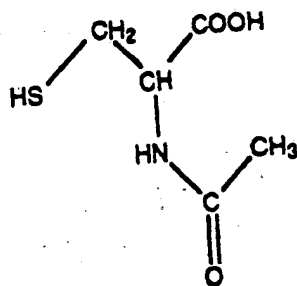
The term halo or halogen includes chloro, fluoro, bromo, and iodo.

The term "enantiomerically enriched composition or compound" refers to a composition or compound that includes at least 95% by weight of a single enantiomer of the compound.

I. N-Acetylcysteine and its Derivatives

Cysteine is an amino acid with one chiral carbon atom. It exists as an L-enantiomer, a D-enantiomer, or a racemic mixture of the L and D enantiomers. The L-enantiomer is the naturally occurring configuration.

N-acetylcysteine (acetamido-mercaptopropionic acid, NAC) is the N-acetylated derivative of cysteine, as illustrated below. It also exists as an L-enantiomer, a D-enantiomer, an enantiomerically enriched composition of one of the enantiomers, or a racemic mixture of the L and D enantiomers. Any of these three forms of NAC can be delivered to the CNS or eye in a lipophilic form for the treatment of pathogenic oxidative processes. In a preferred embodiment, a single isomer of a thioester or thioether of NAC or its salt, and most preferably, the naturally occurring L-enantiomer, is used in the treatment process.



N-acetylcysteine exhibits antioxidant activity (Smilkstein, Knapp, Kulig and Rumack, *N. Engl. J. Med.* 1988, Vol. 319, pp. 1557-62; Knight, K.R., MacPhadyen, K., Lepore, D.A., Kuwata, N., Eadie, P.A., O'Brien, B. *Clinical Sci.*, 1991, Vol. 81, pp. 31-36; Ellis, E.F., Dodson, L.Y., Police, R.J.,

J. Neurosurg., 1991, Vol. 75, pp. 774-779). The
sulfhydryl functional group is a well
characterized, highly reactive free radical
scavenger. In addition, N-acetylcysteine is known
5 to promote the formation of glutathione (a tri-
peptide, also known as g-glutamylcysteinylglycine),
which is important in maintaining cellular
constituents in the reduced state (Berggren, M.,
Dawson, J., Moldeus, P. *FEBS Lett.*, 1984, Vol.
10 176, pp. 189-192). The formation of glutathione
may enhance the activity of glutathione peroxidase,
an enzyme which inactivates hydrogen peroxide, a
known precursor to hydroxyl radicals (Lalitha, T.,
Kerem, D., Yanni, S., *Pharmacology and Toxicology*,
15 1990, Vol.66, pp. 56-61).

Moreover, N-acetylcysteine exhibits properties
other than antioxidant properties that are
beneficial in the treatment of brain and eye trauma
or other disorders. For example, N-acetylcysteine
20 exhibits anti-inflammatory activity (see U.S.S.N.
08/147,864, entitled "Topical Application of a
Lipid Soluble Thioester or Thioether of N-
acetylcysteine for Treatment of Pathological
Conditions Associated with Immune Responses or
25 Inflammatory Conditions").

Other known activities of N-acetylcysteine
include its effectiveness as a mucolytic agent,
wherein the pharmacology is related to the reactive
sulfhydryl group in the molecule (Lightowler and
30 Lightowler, *Arch. Int. Pharmacodyn. Ther.* 1971,
Vol. 189, pp. 53-8). The sulfhydryl group probably
opens sulfide linkages in mucus, thereby lowering
mucosal viscosity. NAC is also used for the
treatment of acetaminophen overdoses (Smilkstein,
35 Knapp, Kulig and Rumack, *N. Engl. J. Med.* 1988,
Vol. 319, pp. 1557-62). A large overdose of
acetaminophen results in a larger portion of the

drug being metabolized via a free radical (cytochrome P-450) pathway which results in hepatic cellular necrosis. N-acetylcysteine, when administered within the first few hours of overdose, protects the liver by acting as an alternate substrate for conjugation with, and detoxification of, the reactive metabolite.

In addition to its mucolytic and free radical scavenging abilities, NAC has been reported to be an effective collagenase inhibitor (Lemp and Roddy, Ann. Ophthalmol. 1974, Vol. 6, pp. 893-5). It has also been reported that NAC reduces the activity of the proteolytic porcine enzymes, leukocyte elastase and pancreatic elastase, by greater than 55% in vitro (Morrison, Burnett and Stockley, *Biol. Chem. Hoppe Seyler* 1986, Vol. 367, pp. 177-82). In yet another capacity, N-acetylcysteine can act as an inhibitor of tumor necrosis factor-alpha production in vivo (Peristeris, P. et al, *Cell. Immunol.* 1992, Vol. 140, pp. 390-99). All of these activities would serve to limit inflammation.

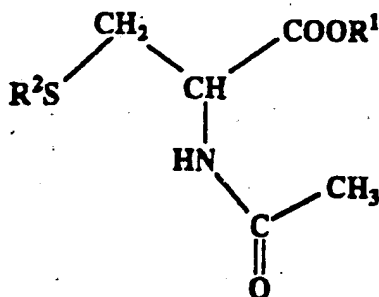
While N-acetylcysteine exhibits beneficial antioxidant and antiinflammatory activity as well as other therapeutic properties, it is not suitable for use in the treatment of CNS or ocular disorders because it is insufficiently lipid soluble to penetrate the blood-brain barrier after systemic (parenteral or oral) administration or the outer tissues of the eye (such as the cornea) after topical administration. The invention disclosed herein focuses on two discoveries: first, NAC can be converted into lipid soluble derivatives that are capable of passing through lipophilic tissue such as that found in the blood-brain barrier and the eye, and second, that the lipid soluble derivative can be broken down in vivo to the active parent compound, NAC at the target location.

The ester or ether moiety of the selected NAC derivative can be either an inert substance or a biologically active substance which itself can have therapeutic benefit for the treatment of pathogenic oxidative damage or associated disorders.

As used herein, the term lipophilic thioester or thioether derivative of N-acetylcysteine refers to any thioester or thioether that is capable of passing through the blood-brain barrier or ocular tissue in a therapeutically effective concentration, and includes but is not limited to either:

(i) any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein; including, or alternatively,

(ii) a compound of the formula:



wherein R¹ is hydrogen, alkyl, aryl, alkaryl, aralkyl, alkyloxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl, an amino acid salt formed by the reaction of the amino group of a naturally occurring amino acid with the carboxylic acid group of the N-acetylcysteine or derivative thereof; an amine salt formed by the reaction of an amine-containing antibiotic with the carboxylic acid group of the N-acetylcysteine, or an inorganic cation, including but not limited to sodium,

potassium, magnesium, calcium, zinc, bismuth, barium, aluminum, copper, cobalt, nickel, and cadmium; and wherein the term amino acid includes but is not limited to alanyl, valinyl, leucinyl, isoleucinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glyciny, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, and histidinyl; and

10 R^2 is alkyl, aryl, alkaryl, aralkyl, alkyloxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl, C(O or S)alkyl, C(O or S)aryl, C(O or S)alkaryl, C(O or S)aralkyl, C(O or S)alkyloxyalkyl, C(O or S)acyloxyalkyl, or

15 phosphate. R^2 can also be the residue of a saturated or unsaturated fatty acid, including but not limited to lauric, oleic, caproic, linoleic, linolenic, caprylic, capric, perlargonic, neononanoic, neodecanoic, palmitelaidoic, myristic,

20 palmitic, stearic, arachidic, behenic, lignoceric, heptanoic, nonanoic, undecanoic, tridecanoic, pentadecanoic, heptadecanoic, nonadecanoic, heneicosanoic, tricosanoic, arachidonic, docosahexanoic, elaidic, erucic, nervonic,

25 palmitoleic or petriselinic acid. Alternatively, R^2 can be the residue of lactic acid, retinoic acid, or ascorbic acid (to form the thioester) or other α -hydroxy acid, or the residue of a dicarboxylic acid (wherein N-acetylcysteine is bound through

30 either or both carboxylic acid groups), including but not limited to cromolyn, nedocrimil, or other mast cell stabilizers, azelaic acid, or methotrexate. In yet another embodiment, R^2 is the residue of sebacic acid, phthalic acid,

35 terephthalic acid, isophthalic acid, adipic acid, 1,10-dodecanoic acid, bis(p-carboxyphenoxyalkane), fumaric acid, 1,4-diphenylenediacrylic acid,

branched monomers such as 1,3,5-benzenetricarboxylic acid, azeleic acid, pimelic acid, suberic acid (octanedioic acid), itaconic acid, biphenyl-4,4'-dicarboxylic acid, and
5 benzophenone-4,4'-dicarboxylic acid, p-carboxyphenoxyalkanoic acid, hydroquinone-O,O-diacetic acid, 1,4-bis-carboxymethyl benzene, 2,2-bis-(4-hydroxyphenyl)propane-O,O-diacetic acid, 1,4-phenylene-dipropionic acid, and cyclohexane
10 dicarboxylic acid (wherein N-acetylcysteine is bound through one or more carboxylic acid groups to form thioesters). R^2 can also be the residue of another active molecule such as vitamin D (including but not limited to $1\alpha,25$ -dihydroxy
15 vitamin D_3 , 1α -hydroxy vitamin D_3 , ($1\alpha,24,25$)-trihydroxy vitamin D_3 , and ($1\alpha,25,26$)-trihydroxy vitamin D_3) and other derivatives of vitamin D_3 , including but not limited to hydroxylated, alkylated and acylated derivatives thereof, and
20 vitamin E, where the formation of a variety of thioether or ester bonds is possible, all of which are intended to fall within the scope of the invention.

Non-limiting examples of amine-containing
25 antibiotics that can be used to form a salt with N-acetylcysteine include, but are not limited to, erythromycin, propionylerythromycin, neomycin, gentomycin, mechlloclclin, tobramycin, and kanamycin.

30 NAC that contains a combinations of R^1 and R^2 as described herein can be used for the delivery of N-acetylcysteine to prevent or minimize pathogenic oxidative damage or associated disorders, as well as combinations of NAC derivatives.

35 To counteract the harmful effects of the some of the oxidative processes described above, including but not limited to free radical mediated

lipid peroxidation, the body naturally produces a number of defensive compounds such as α , β - and γ -tocopherols (vitamin E, which is an antioxidant), ascorbic acid, catalase, superoxide dismutase, glutathione, glutathione peroxidase, glutathione reductase, and other compounds and enzymes.

Vitamin E is known to be a scavenger of both lipid peroxy radicals and oxygen radicals, as well as to have a membrane-stabilizing action. It is believed that chronic dietary vitamin E supplementation can attenuate postischemic cerebral hypotension by inhibiting the lipid peroxidative process. Therefore, in one preferred embodiment, a thioester or thioether of NAC is provided in which the thioester or thioether moiety is one of the materials naturally used by the body to minimize oxidative damage, including but not limited to an enzyme, vitamin, or other biological molecule with antioxidantizing properties or that mediates antioxidantizing processes. If necessary, the material can be linked to NAC through a biodegradable linking moiety, as well known to those of skill in the art of organic synthesis and biochemistry.

II. Pharmaceutical Compositions of NAC

Humans, equine, canine, feline, bovine, ovine and other animals, and in particular, mammals, subject to, or at risk of, pathogenic oxidative processes in the central nervous system or eye can be treated by delivery of an effective amount of N-acetylcysteine or a pharmaceutically acceptable derivative or salt, administered as a lipid soluble thioester or thioether thereof, optionally in a pharmaceutically acceptable carrier or diluent.

As used herein, the term pharmaceutically

acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal undesired toxicological effects.

5 Pharmaceutically acceptable carboxylic acid and mercaptyl salts are known to those skilled in the art, including inorganic salts with cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium,
10 potassium, and the like, or with a cation formed with a nitrogenous base such as ammonia, N,N-dibenzylethylene- diamine, D-glucosamine, or ethylenediamine.

In general, the derivatives of N-
15 acetylcysteine disclosed herein are "prodrugs" of N-acetylcysteine, that are either active in the prodrug form or are cleaved in vivo to provide the parent NAC as well as an inert or active ester or ether moiety. Modifications of the active
20 compound can affect the bioavailability and rate of metabolism of the active species, thus providing control over the delivery of the active species through the blood-brain barrier or ocular tissue. For example, it is well known in the art that
25 various modifications of the active molecule, such as alteration of charge, can effect water and lipid solubility and thus alter the potential for crossing the blood-brain barrier. Further, the modifications can affect the bioactivity of the
30 compound, in some cases increasing the activity over the parent compound or increasing the permeability of the parent compound through the blood-brain barrier. This can easily be assessed by preparing the derivative and testing its
35 activity according to the methods described herein, or other method known to those skilled in the art. Preferred derivatives of this sort include, but are

not limited to the residues of oleic acid (S-oleoyl-N-acetyl-L-cysteine), lauric acid (S-lauryl-N-acetyl-L-cysteine), myristic acid (S-myristoyl-N-acetyl-L-cysteine), capric acid (S-caprolyl-N-acetyl-L-cysteine), retinoic acid (S-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6, 8-nonatetraenoyl-N-acetyl-L-cysteine), lactic acid (S-lactoyl-N-acetyl-L-cysteine) and other α -hydroxy acids, ascorbic acid (S-ascorboyl-N-acetylcysteine), and NAC derivatives of vitamin E, vitamin D, or other enzymes, vitamins, or other biological molecules with antioxidizing properties or that mediate antioxidant processes.

Solutions or suspensions used for parenteral, intra-dermal, or subcutaneous administration can include, for example, the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; anti-bacterial agents such as benzyl alcohol or methyl parabens; anti-oxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount of the drug without causing serious toxic effects in the patient treated. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The concentration of active compound in the

drug composition will depend on absorption, distribution, deactivation, and excretion rates of the drug as well as other factors known to those of skilled in the art. Dosage values will also vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. The concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient can be administered at once, or can be divided into a number of smaller doses to be administered at varying time intervals.

The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, anti-fungals, anti-inflammatories, disinfectants, or anti-viral compounds.

One preferred mode of administration of the NAC derivative active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients,

or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents. The NAC derivative can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any components typically used in formulation, for example, a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose

vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

5 When used for ocular therapy, the NAC derivative is administered in an inert vehicle to eye tissue by intraocular injection or topically. The term "inert vehicle" refers to any vehicle that is inert to both the NAC derivative and to the
10 host, and can includes adjuvants, preservatives, buffers, and demulcents. As used herein, "ophthalmically effective amount" is that amount which in the composition administered and by the technique administered, provides an amount of
15 therapeutic agent to the involved eye tissues sufficient to improve visual function or prevent or minimize its loss for a desired period of time.

 When the intraocular injection is subconjunctival, an ophthalmically effective amount
20 of NAC derivative is administered typically in a polymeric carrier such as a dextran or polysorbate 80, with that optionally contains additives such as disodium edentate, sodium sulfite, and/or sodium chloride, and sodium hydroxide or hydrogen chloride
25 for pH adjustment. When the intraocular injection is intracameral or intravitreal, an effective amount of NAC derivative is typically administered in a vehicle containing phosphate buffered saline, citrate buffered saline, or chrondrotin sulfate, or
30 in a polymeric vehicle such as sodium hyaluronate, or hyaluronic acid, purified polyacrylamide or polysorbate 80, with the formulation containing sodium hydroxide or hydrogen chloride for pH adjustment.

35 When the administration is topical, a topical formulation containing an effective amount of a NAC derivative is administered typically in an aqueous

5 solution that can include polymers, aqueous suspension, ointment, gel or cream vehicle. Except for ointments, these vehicles may contain liposomes for creating a reservoir of dissolved agent for contact with the tear film.

10 Topical administration is preferable when the target of the treatment is located in or near the anterior chamber of the eye. By contrast, because the flow of aqueous humor is from the ciliary body (behind the iris) forward towards the cornea before it exists through the trabecular meshwork and Schlemm's canal, penetration of drugs to the back of the eye when administered topically to the front of the eye occurs with difficulty. It is therefore
15 often more effective to administer drugs intended for the treatment of uveal and retinal diseases by the systemic route where access to the eye occurs through the choroid plexus, or by the intravitreal route. Some of the more severe eye diseases affect
20 those targets which are difficult to treat effectively by the topical route and these diseases can be associated with markedly impaired vision or blindness. Accordingly, the topical route is preferred for the convenience of individual patient
25 self-administration, whereas the intraocular or systemic routes are preferred for surgical and presurgical administration.

30 In order to maintain an ocularly adequate therapeutic level of drug in the back of the eye in these instances where surgery is not involved, or has been concluded, the present invention also contemplates the treatment of an ophthalmic disease by administration of a therapeutically effective amount of the NAC derivative in a suitable carrier,
35 by oral, intramuscular and intravenous routes, in addition to the convenient topical route or by intraocular injection.

To administer the intravenous formulation for treatment of the eye, the drug formulations are preferably dose injected or infused into a major vein (e.g., in the arm), or are introduced by continuous intravenous drip.

Intramuscular formulations will typically include an effective amount of the NAC derivative in an aqueous solution or suspension for intramuscular delivery, and can include, for example, polysorbate 80, methyl cellulose, and other demulcents. Other additives desirably added to intramuscular formulations include sodium chloride and sodium bisulfite. To administer the intramuscular formulations for treatment of the eye, the drug formulations will be injected, for example, into the upper outer quadrant of the gluteal muscle.

III. Synthesis and Chemical Properties of Derivatives of N-Acetylcysteine

Thioester and thioether derivatives of NAC can be easily prepared using standard methods known to organic chemists.

One synthetic route for the formation and purification of the thioester derivatives of N-acetylcysteine described herein is outlined below.

N-acetylcysteine in dry tetrahydrofuran (THF) is stirred under inert atmosphere. One equivalent of triethylamine is added and the reaction mixture is chilled to 5°C. One equivalent of the desired acid chloride, dissolved in THF, is added slowly to the reaction mixture. After addition, the reaction mixture is stirred for three hours, and reaction progress monitored by thin-layer chromatography until the reaction approaches completion.

Desired acid chlorides are formed by the addition of an excess of thionyl chloride to the

fatty acid (for example) under inert, dry conditions according to methods known to those skilled in the art.

5 Thioethers can be formed using a variety of synthetic methods known to those skilled in the art, including by the Williamson ether synthesis, wherein N-acetylcysteine is combined with sodium (solid) and further reacted with an alcohol.

10 Functional groups can be protected as necessary, as known to those skilled in the art. See, for example, Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991. For example, the hydroxy group in the α -hydroxy acids must be protected
15 prior to reaction with thionyl chloride, and subsequent reaction with N-acetylcysteine. Once the thioester is formed, the hydroxyl group can then be de-protected.

20 **IV. Method of evaluating the penetration of N-acetylcysteine through the blood-brain barrier and into the eye.**

The ability of a thioester or thioether derivative to minimize pathogenic oxidation damage can be measured in a variety of ways, including by
25 examining their effect on CNS oxygen toxicity in rats (for details of the assay, see Lalitha, T., et al., *Pharmacology and Toxicology*, 1990, 66, 56-61).

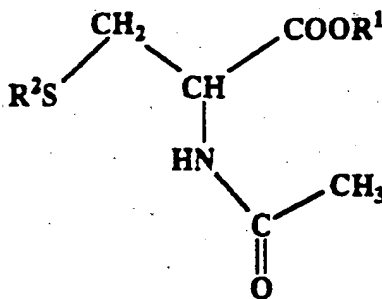
Briefly, rats are exposed to high pressures
30 of oxygen for up to 60 minutes. After a recovery period (about one week) during which the animals are treated with the test drugs through various routes of administration, they are re-exposed to oxygen under similar conditions to the initial
35 exposure. The oxidative damage to the CNS is measured through previously implanted electrodes by the time of appearance of the first electrical

discharge (FED) on ECoG recorder.

The concentrations of N-acetylcysteine, its derivatives and metabolites can also be measured in brain, spinal cord, eyes, blood and other organs to assess biodistribution. After sacrifice, the blood is collected and brain, spinal cord, eyes and lungs, and a portion of the liver, are immediately collected and frozen. These organs are homogenized in buffer at pH 7.5. Concentration of N-acetylcysteine and its derivatives is carried out by high pressure liquid chromatography as known to those skilled in the art. Glutathione is determined as non-protein sulfhydryl in the deprotonized tissue or blood filtrates according to the method of Beutler (Beutler, E.: Red Cell Metabolism: A Manual of Biochemical Methods, Grune & Stratton, New York, 1975, 2nd edition).

We claim:

1. A method for treatment of pathogenic oxidation processes in the central nervous system comprising administering an effective amount of a compound of the formula:



wherein R¹ is hydrogen, alkyl, alkaryl, aralkyl, alkoxyalkyl aryloxyalkyl, and amino acid salt formed by the reaction of the amino group of a naturally occurring amino acid with the carboxylic acid group of the N-acetylcysteine; or an amine salt formed by the reaction of an amine-containing antibiotic with the carboxylic acid group of the N-acetylcysteine, or an inorganic cation, and

R² is alkyl, aryl, aralkyl, alkyloxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl, C(O or S) alkyl, C(O or S) aryl, C(O or S) alkaryl, C(O or S) aralkyl, C(O or S) alkyloxyalkyl, C(O or S) acyloxyalkyl, phosphate, or an inorganic cation; the thioester formed between N-acetylcysteine and the residue of a saturated or unsaturated fatty acid, the residue of lactic or other α-hydroxy acids, retinoic acid, or ascorbic acid; or the residue of an alkyl or aromatic dicarboxylic acid;

or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically

acceptable carrier for systemic administration.

2. The method of claim 1 wherein the compound is administered several times a day.

3. The method of claim 1 wherein R^1 is an amino acid.

4. The method of claim 3 wherein R^1 is an amine-containing antibiotic.

5. The method according to claim 4 wherein the antibiotic is selected from the group consisting of erythromycin, propionylerythromycin, neomycin, gentomycin, tobramycin, and mechlocycline.

6. The method of claim 1 where R^1 or R^2 is an antioxidant.

7. The method of claim 6 where the antioxidant is selected from the group consisting of ascorbic acid or vitamin E or derivatives.

8. The method of claim 1 where R^1 or R^2 is a free radical scavenger.

9. The method according to claim 1 wherein R^2 is a fatty acid residue.

10. The method according to claim 9 wherein the fatty acid is selected from the group lauric, oleic, caproic, linoleic, linolenic, caprylic, capric, myristic, palmitic, steric, arachadic, behenic, lignoceric, heptanoic, nonanoic, undecanoic, tridecanoic, pentadecanoic, heptadecanoic, nonadecanoic, heneicosanoic, tricosanoic, arachadonic, docosahexanoic, elaidic, erucic, nervonic, palmitoleic or petriselinic acid.

11. The method of claim 8 where the preferred acid residue is from the group consisting of lauric or oleic acid.

12. The method according to claim 1 wherein the mammal is a human.

13. The method of claim 1 wherein the compound is administered in a concentration between

0.001 and 50 mg/kg/day.

14. The method of claim 1 wherein the compound is administered in a controlled release formulation.

15. The method of claim 1 wherein the compound is administered in combination with another compound or compounds selected from the group consisting of antivirals, antibiotics, anti-inflammatories, and immunosuppressants.

16. The method of claim 1 wherein the compound also has anti-inflammatory activity.

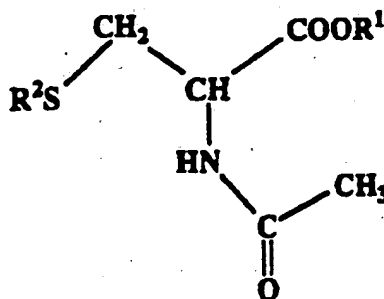
17. The method of claim 1 wherein the compound also has immunosuppressive activity.

18. The method of claim 1 wherein the compound also has antioxidant activity.

19. The method of claim 1 wherein the compound also has free radical scavenging activity.

20. The method of claim 1 wherein the compound is selected from the group consisting of (S-oleoyl-N-acetyl-L-cysteine), (S-lauryl-N-acetyl-L-cysteine), (S-myristoyl-N-acetyl-L-cysteine), (S-caproyl-N-acetyl-L-cysteine), (S-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenol-N-acetyl-L-cysteine), (S-ascorbyl-N-acetyl-L-cysteine) and (S-lactoyl-N-acetyl-L-cysteine).

21. A method for treatment of pathogenic oxidation processes in the eye comprising administering an effective amount of a compound of the formula:



wherein R¹ is hydrogen, alkyl, alkaryl, aralkyl, alkoxyalkyl aryloxyalkyl, and amino acid salt formed by the reaction of the amino group of a naturally occurring amino acid with the carboxylic acid group of the N-acetylcysteine; or an amine salt formed by the reaction of an amine-containing antibiotic with the carboxylic acid group of the N-acetylcysteine, or an inorganic cation, and

R² is alkyl, aryl, aralkyl, alkyloxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl, C(O or S) alkyl, C(O or S) aryl, C(O or S) alkaryl, C(O or S) aralkyl, C(O or S) alkyloxyalkyl, C(O or S) acyloxyalkyl, phosphate, or an inorganic cation; the thioester formed between N-acetylcysteine and the residue of a saturated or unsaturated fatty acid, the residue of lactic or other α -hydroxy acids, retinoic acid, or ascorbic acid; or the residue of an alkyl or aromatic dicarboxylic acid;

or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier for systemic administration.

22. The method of claim 21 wherein the compound is administered topically.

23. The method of claims 1 or 21 wherein the compound is administered orally.

24. The method of claims 1 or 21 wherein the compound is administered intramuscularly.

25. The method of claims 1 or 21, wherein the compound is administered intravenously.

26. The method of claim 21, wherein the compound is administered by intraocular injection.

27. The method of claim 21 wherein R¹ is an amine-containing antibiotic.

28. The method of 27 wherein the antibiotic is selected from the group consisting of erythromycin, propionylerythromycin, neomycin,

gentomycin, tobramycin, and mechlencycline.

29. The method of claim 21 where R^1 or R^2 is an antioxidant.

30. The method of claim 29 where the antioxidant is selected from the group consisting of vitamin E, vitamin D, and ascorbic acid.

31. The method of claim 1 or 21, wherein R^1 or R^2 is a biological molecule or enzyme that mediates antioxidant processes.

32. The method of claim 21 where R^1 or R^2 is a free radical scavenger.

33. The method according to claim 21, wherein R^2 is a fatty acid residue.

34. The method according to claim 33 wherein the fatty acid is selected from the group lauric, oleic, caproic, linoleic, linolenic, caprylic, capric, myristic, palmitic, steric, arachadic, behenic, lignoceric, heptanoic, nonanoic, undecanoic, tridecanoic, pentadecanoic, heptadecanoic, nonadecanoic, heneicosanoic, tricosanoic, arachadonic, docosahehexanoic, elaidic, erucic, nervonic, palmitoleic or petriselinic acid.

35. The method of claim 33 where the acid residue is selected from the group consisting of lauric or oleic acid.

36. The method of claim 21 wherein the mammal is a human.

37. The method of claim 21 wherein the compound is administered in a concentration between 0.001 and 50 mg/kg/day.

38. The method of claim 21 wherein the compound is administered in a controlled release formulation.

39. The method of claim 21, the compound is administered in combination with another compound or compounds selected from the group consisting of antivirals, antibiotics, anti-inflammatories, and

immunosuppressants.

40. The method of claim 21, wherein the compound also has anti-inflammatory activity.

41. The method of claim 21, wherein the compound also has immunosuppressive activity.

42. A pharmaceutical composition comprising an effective amount of a compound described in claim 1 to treat a pathogenic oxidation process in the central nervous system of a mammal in a pharmaceutically acceptable carrier.

43. A pharmaceutical composition comprising an effective amount of a compound described in claim 1 to treat a pathogenic oxidation process in the eye of a mammal in a pharmaceutically acceptable carrier.

44. The pharmaceutical composition of claims 42 or 43, wherein the carrier is suitable for systemic delivery.

45. The composition of claim 43 that is suitable for topical delivery.

46. The composition of claims 42 or 43 wherein the carrier is suitable for oral delivery.

47. The composition of claims 42 or 43 wherein the carrier is suitable for intramuscular delivery.

48. The composition of claims 42 or 43 wherein the carrier is suitable for intravenous delivery.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/14981

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A61K 31/70, 31/195, 31/205. US CL : 514/29, 400, 554, 562. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/29, 400, 554, 562. Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS SEARCH TERMS: PATHOGENIC OXIGENATION, ERYTHROMYCIN, PROPIONYLERYTHROMYCIN.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,970,236 (ZIGGIOTTI ET AL) 13 NOVEMBER 1990, COLUMN 1, LINES 11-41.	1-48
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 06 APRIL 1995	Date of mailing of the international search report 25 APR 1995	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer THEODORE J. CRIARES Telephone No. (703) 308-1235	

Powered by  DIALOG**Treatment of pathogenic oxidn. process in central nervous system - by admin. of lipid soluble thioesters or thioethers of N-acetyl-cysteine****Patent Assignee:** ARCTURUS PHARM CORP**Inventors:** ARNDT K A; GALLI S J; MCALOON M H; SHARPE R J**Patent Family**

Patent Number	Kind	Date	Application Number	Kind	Date	Week	Type
WO 9517900	A1	19950706	WO 94US14981	A	19941229	199537	B
AU 9514470	A	19950717	AU 9514470	A	19941229	199544	

Priority Applications (Number Kind Date): US 93175959 A (19931230)**Patent Details**

Patent	Kind	Language	Page	Main IPC	Filing Notes
WO 9517900	A1	E	35	A61K-031/70	
Designated States (National): AM AU BB BG BR BY CA CN CZGE HU JP KG KP KR KZ LK LT LV MD MG MN NO NZ PL RO RU SI SK TJ TT UA UZ VN					
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ					
AU 9514470	A			A61K-031/70	Based on patent WO 9517900

Abstract:

WO 9517900 A

Treatment of pathogenic oxidn. processes in (i) the central nervous system or (ii) the eye, comprises admin. of an N-acetylcysteine deriv. of formula $R_2S-CH_2-CH(COOR_1)-NH-COMe$ (I) or its salt, opt. in a carrier for systemic admin. $R_1 = H$, alkyl; alkaryl; aralkyl; alkoxyalkyl; aryloxyalkyl; an amino acid salt formed by reaction of the amino gp. of a naturally occurring amino acid with the carboxylic acid gp. of the N-acetylcysteine; or an amine salt formed by reaction of an amine-contg. antibiotic with the carboxylic acid gp. of the N-acetylcysteine; or an inorganic cation; $R_2 =$ alkyl; aryl; aralkyl, alkyloxyalkyl; aryloxyalkyl; C(O or S)- alkyl; C(O or S)-aryl; C(O or S)-alkaryl; C(O or S)-aralkyl; C(O or S)- alkoxyalkyl; C(O or S)-acyloxyalkyl; phosphate, an inorganic cation; etc.

USE - The processes may be used for the treatment of, e.g. Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, ocular injury, diabetic retinopathy, cataract formation, glaucoma, inflammatory eye disease or bullous keratitis.

ADVANTAGE - The cpds. are lipid soluble.

Dwg. 0/0

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